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Mifepristone: Treatment of Cushing's Syndrome

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Cushing's syndrome is mediated by glucocorticoid receptors and results from chronic exposure to excessive endogenous or exogenous glucocorticoids. If endogenous glucocorticoids are present in excess, this surplus is a consequence of excessive production rather than inadequate destruction. Although the adrenal cortex is the sole source of endogenous glucocorticoid production, pathologic elevation of glucocorticoid secretion may result from an autonomously functioning adrenal cortex or from an excessive production of adrenocorticotrophin hormone (ACTH). Although ACTH is ordinarily derived from the anterior pituitary, pathologic secretion of ACTH (and its variants) may be derived either from the pituitary or an ectopic source.

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The treatment of endogenous Cushing's syndrome requires diagnosis of the pathophysiologic source, with subsequent treatment being directed toward the underlying problem. Surgical extirpation of the underlying cause is the treatment of choice, whether the cause is an adrenal neoplasm, a pituitary adenoma, or an ectopic ACTH-secreting tumor. In some cases, however, the underlying cause may not be amenable to a surgical resection. Examples include pituitary tumors that have involved the cavernous sinus, occult or metastatic ectopic ACTH-secreting tumors, and metastatic adrenocortical carcinoma. In such cases, the clinician may be confronted with considering complete removal of the adrenal glands, pituitary irradiation, or pharmacologic therapy to blunt cortisol secretion or action. Additionally, pharmacologic therapy of endogenous Cushing's syndrome also may be indicated under other conditions (i.e., acute psychiatric problems de-

veloping as a consequence of glucocorticoid excess or life-threatening opportunistic infection).

Several pharmacologic means exist for control of excessive glucocorticoid secretion. These include metyrapone, aminoglutethimide, mitotane, ketoconazole, or mifepristone (RU 486; Roussel-Uclaf, Romainville, France). All of these therapeutic agents, except mifepristone, operate by decreasing adrenal steroid secretion. Mifepristone functions as a glucocorticoid antagonist by binding to glucocorticoid receptors. It actions and use will be covered in more detail.

Mifepristone as a Glucocorticoid Antagonist and Agonist

Mifepristone (RU 486 or RU 38486) was originally developed by Roussel-Uclaf as an antiprogestin, and this antihormonal action has been the primary focus of most clinical studies. The activity of mifepristone as a glucocorticoid antagonist, however, was recognized early in the stages of drug development with the first report of antiglucocorticoid activity by Philibert et al. in 1981.[1] After demonstration of the antiglucocorticoid activity in primates,[2] studies in humans were initially reported in 1984 by Bertagna and colleagues.[3] In the Bertagna studies, antiglucocorticoid activity was demonstrated by a marked increase in plasma cortisol and lipotropin after administering 400 mg of mifepristone to "normal" men. In addition, mifepristone administration was associated with a dose-dependent blockade of dexamethasone-induced cortisol suppression. Thus mifepristone was shown to act as an anti-glucocorticoid by antagonizing the negative feedback on the pituitary of endogenous and exogenous glucocorticoids. Reports of mifepristone's

Like many receptor-binding compounds, mifepristone exhibits mixed antagonist/agonist activity. In a carefully conducted trial examining the glucocorticoid agonist-like activity of mifepristone in humans, plasma ACTH responses and cortisol responses were monitored in the presence and absence of corticotropic releasing hormone stimulation in patients with primary adrenal insufficiency after a brief period (36 hours) of glucocorticoid deprivation. Under these circumstances, oral mifepristone administration (20 mg/kg) resulted in a partial suppression of the corticotropic releasing hormone-induced ACTH response.[4] These data strongly suggest that mifepristone exerts some agonistic effect at the glucocorticoid receptor. The glucocorticoid agonist potency of mifepristone in these experiments was calculated to be approximately 1/250th the activity of cortisol (on a weight basis). In a subsequent series of experiments in primates, mifepristone was unable to provide adequate agonist activity to prevent fatal adrenal insufficiency in adrenalectomized-monkeys.[5] Thus, although glucocorticoid agonist activity is detectable in sensitive assays, glucocorticoid antagonism is the predominant action. However, glucocorticoid antagonism in patients occurs at higher doses in patients than does progesterone antagonism, and women who have received mifepristone as an antiprogestin in early pregnancy typically report no ill effects due to glucocorticoid antagonism.

Mifepristone exerts its glucocorticoid antagonism by occupying glucocorticoid receptors, thereby blocking in a competitive fashion agonist-induced transcriptional activation. The affinity of mifepristone for the glucocorticoid receptor is approximately three-fold higher than that for dexamethasone.[1] The mechanism whereby mifepristone acts at the glucocorticoid receptor is

length and varying actions), whereas the glucocorticoid receptor typically exists in only one isoform. In the antagonism of progesterone receptors, mifepristone avidly binds to the receptor and operates primarily at a post-DNA binding step. In glucocorticoid antagonism, mifepristone has at least two mechanisms of action. Although it also can act at a post-DNA binding step after binding to the receptor, binding of mifepristone to cytosolic glucocorticoid receptors has the additional effect of blocking translocation of glucocorticoid receptors to the nucleus.[6] The end result is that mifepristone-bound glucocorticoid receptors are relatively segregated from DNA binding, and even when DNA binding occurs, transcriptional activation is significantly diminished in comparison to agonist-bound receptors.

The clinical pharmacology of mifepristone is described elsewhere in this publication. Mifepristone is readily absorbed after oral ingestion with a bioavailability exceeding 30%. Peak drug levels are typically reached in 1–2 hours, and the drug has a half-life of more than 20 hours. Mifepristone is highly protein bound, extensively metabolized, and primarily excreted in the bile. Mifepristone metabolites also exhibit a prolonged half-life and biologic activity.[7,8]

Treatment of Cushing's Syndrome With Mifepristone

The first report of mifepristone treatment of Cushing's syndrome was a case report published in 1985.[9] In this report, a patient with inoperable ectopic ACTH secretion secondary to a metastatic carcinoid tumor was treated in a step-dose fashion starting at 5 mg/kg/day by mouth and escalating by 5 mg/kg every 1–2 weeks. The maximum dose of mifepristone administered was 20 mg/kg/day. Before mifepristone treatment, the patient failed to respond to therapy with metyrapone and had many manifestations

libido, muscle weakness, round facies, dorsocervical fat pads, central obesity, weight gain, hypertension, hypokalemic alkalosis, abnormal glucose tolerance test results, increased urinary nitrogen excretion, increased urinary and plasma cortisol, and increased ACTH. During therapy with mifepristone, all objective manifestations of Cushing's improved except for total body weight, plasma and urinary cortisol, and plasma ACTH. During mifepristone therapy, the circulating ACTH level increased further. All psychological measures also improved according to the patient's report and psychiatric interviews. The patient was treated for a total of 10 weeks without recognized side effects. After this time, limited drug availability prevented further treatment, and the patient received a bilateral adrenalectomy. This important case report demonstrated the feasibility of treating Cushing's syndrome patients with mifepristone.

The next report of mifepristone administered to patients with Cushing's described 3 days treatment in seven patients.[10] Five patients had been diagnosed with pituitary-dependent Cushing's syndrome (Cushing's disease); two patients had ectopic secretion of ACTH. In each of the five patients with Cushing's disease, 3 days of mifepristone (400 mg/day) were associated with marked increases in urinary cortisol, which persisted for 3–4 days after drug discontinuation. Plasma cortisol, urinary 17-hydroxysteroids, and plasma lipotropin also were increased, but to a lesser extent. These data suggest that mifepristone antagonized the glucocorticoid mediated suppression of ACTH secretion at the level of the pituitary tumor. One patient developed nausea and headaches; another developed lethargy. Each of these patients were treated with dexamethasone and improved within minutes according to the report. In the two patients with ectopic ACTH secreting tumors

cocorticoid feedback inhibition on ectopic ACTH-secreting tumors.

These studies by Bertagna and colleagues[10] helped to highlight two important potential problems of treating patients with pituitary-dependent Cushing's syndrome with mifepristone. Blockade of glucocorticoid action results in increased cortisol secretion, probably as a result of decreased feedback of glucocorticoids on the pituitary. This decreased feedback leads in turn to increased ACTH secretion and increases cortisol, which competes with mifepristone at the glucocorticoid receptor. Previous studies have shown that hyperplastic adrenals can vigorously respond to even small changes in ACTH, and this appeared to have occurred in these patients. Secondly, because there is no acceptable rapid biochemical measurement to monitor glucocorticoid action (as opposed to secretion), titration of mifepristone dosing may be problematic. A particular concern is that excessive receptor blockade may produce symptoms of adrenal insufficiency despite high cortisol levels.

In the largest series reported to date, 11 patients with Cushing's syndrome due to inoperable adrenal cancer or inoperable "ectopic" ACTH-secreting neoplasms were treated with mifepristone.[11] Doses varied from 5 to 22 mg/kg/day, and treatment durations varied from 4 weeks to 12 months. Seven of the 11 patients demonstrated marked improvement in the syndrome as manifested by improvement in the Cushingoid phenotype, psychiatric status, hypertension, and carbohydrate intolerance. In this study, three patients discontinued mifepristone because of possible signs or symptoms of adrenal insufficiency. One additional patient developed an unrelated medical complication and discontinued treatment for reasons unrelated to the drug. Nausea was the most common complaint; two of the three male patients developed toms had a significant decrease in cortisol secretion for reasons that were unclear. From these data, the authors conclude that mifepristone has clinical use in the treatment of a subset of patients with Cushing's syndrome whose cortisol secretion depends on non-pituitary sources. Clinical manifestations of adrenal insufficiency may be encountered in a substantial minority of patients, and (again) management was complicated by a lack of reliable biochemical markers of glucocorticoid action.

In a more recent report, two patients with acute psychosis and high elevations of cortisol were treated with treated with mifepristone.[12] In the first case, a 43-year-old with adrenal cancer and psychosis was treated with 800 mg/day of mifepristone and all mental abnormalities resolved within 24 hours. After 5 days, hypoglycemic episodes appeared and the mifepristone dose was decreased to 400 mg/day without additional complications. A second patient, also with inoperable adrenal cancer and psychosis, was treated with 400 mg/day mifepristone with complete disappearance of psychiatric symptoms within 24 hours. Other signs and symptoms of Cushing's improved during the remaining 2 months of the patient's life and the patient did not develop Addisonian-type complications.

Summary

Mifepristone is a potent antagonist of glucocorticoid and progesterone receptors. It is the only drug administered to humans with these actions. Exploration of mifepristone in the treatment of Cushing's syndrome is in its infancy. The cases reviewed in this report comprise the entire medical literature. Development and availability of mifepristone has been severely restricted because of controversy surrounding its ability to function as an "abortion pill." As

Although the authors have highlighted therapeutic trials with the drug, they also note that diagnostic uses in cases of glucocorticoid excess may be of interest. Some cases of endogenous Cushing's syndrome are difficult to diagnosis and a glucocorticoid antagonist may be as useful as a glucocorticoid agonist (such as dexamethasone) in the dynamic evaluation of glandular function. In particular, mifepristone might be useful in distinguishing pituitary from occult ectopic ACTH-secreting tumors.

One of the primary problems surrounding the use of mifepristone in cases of Cushing's syndrome is the long half-life of the drug and the necessity to titrate doses carefully in a manner that avoids signs and symptoms of glucocorticoid deficiency. Biochemical markers reflecting the "glucocorticoid status" of a patient would be useful for dose adjustment and monitoring and would improve the risk to benefit ratio for mifepristone treatment of Cushing's syndrome.

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